Post-traumatic stress disorder after cancer diagnosis in adults: A meta-analysis

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Short title: Meta-analysis on PTSD after cancer diagnosis

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Abstract

BACKGROUND: Since the introduction of serious illness as a potential traumatic stressor in the fourth version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), research on the prevalence and predictors of post-traumatic stress disorder (PTSD) after cancer diagnosis has proliferated. Studies have reported widely varying estimates of the number of people with PTSD after cancer. The aim of this review is to synthesize quantitative data from studies reporting the proportion of people with PTSD among groups of cancer survivors. METHODS: We undertook a diversified literature search strategy and identified 120 samples from 110 sources reporting a proportion of cancer survivors with PTSD. Of these, eleven studies, containing twelve samples, reported estimates of PTSD in cancer survivors compared to matched controls. RESULTS: A random effects meta-analysis estimated the odds ratio as 1.66 (95% confidence interval: 1.09 to 2.53) for PTSD in cancer survivors compared to controls, although some of this apparent increase may have arisen from publication bias. Factors influencing the reported proportion of a post-cancer sample with PTSD included measurement type (clinical interview vs. self-report instrument), type of cancer, type of treatment, geographic region, whether the term "post-traumatic stress" was in the title or abstract, prior trauma, age, and time since diagnosis. CONCLUSIONS: PTSD, diagnosed according to DSM-IV criteria, is more common in survivors of cancer than it is in the general population. Estimates of the occurrence of PTSD in patients with a history of cancer depend upon clinical and demographic factors, as well as upon study design.

Introduction

Psychological distress and morbidity may be triggered or exacerbated by a cancer diagnosis. Along with financial problems, role reversals, and the physical consequences of treatment [1-3], cancer survivors face a variety of psychological sequelae of their disease, including loneliness and fear of recurrence [4; 5]. Although much attention has focused on depression and anxiety after cancer diagnoses, a recent systematic review found that cancer survivors have no increased risk of depression and only 1.27 times the relative risk of anxiety compared to control participants [6].

Cancer may cause psychological morbidity in the form of post-traumatic stress disorder (PTSD). PTSD is said to arise from an inadequate cognitive processing of trauma memories [7]. Symptoms include: re-experiencing during flashbacks or intrusive thoughts; avoidance of trauma memories coupled with emotional numbing; hyperarousal symptoms, such as an exaggerated startle response [8]. A diagnosis of serious illness was listed as one potential traumatic stressor in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM) [8]. Cancer fits both of the DSM-IV criteria for a traumatic stressor; it is life-threatening and may trigger "intense fear, horror, and helplessness" [8]. Newer DSM-5 criteria focus on the medium and duration of the trauma while excluding any characterization of its subjective experience, but according to the DSM-5, a medical illness such as cancer is only considered a traumatic event when it is "sudden" and "catastrophic" [9]. Furthermore, there have been a number of changes to the formulation of a PTSD diagnosis in DSM-5 which might impact on its applicability within a cancer setting; for instance, the three symptoms described in the DSM-IV have now been divided into four, including a new category of "negative cognitions."

Apart from this, there are a number of conceptual issues surrounding the inclusion of cancer within a traumatic stress framework. As Kangas et al. [10], Smith et al. [11], and Gurevich et al. [12] discuss, the cancer experience may involve multiple traumatic events over the course of diagnosis and treatment, some of which are complex and repeated. Furthermore, cancer may be considered an "internal" threat, rather than an external threat from, for example, attackers or natural disasters [10; 12; 13]. Whether an internal threat to one's health can function as a trauma is controversial. Gurevich et al. [12] and Mehnert and Koch [14] argue that some of the most distressing aspects of the cancer experience are those that involve uncertainty or a fear of potential death in the future, rather than discrete external traumatic events taking place in the past; nevertheless, Mehnert et al. [14] also found that diagnosis itself, a discrete event, is often perceived as traumatic.

Furthermore, some of the symptoms of PTSD, such as a loss of concentration or insomnia, may be attributable to cancer or its treatment [10; 12]. As Smith et al. [11] discuss, cancer also differs from other types of traumatic stressors in that its "threat," or risk of pain, death, or injury, varies considerably from case to case. Rustad et al. [15] have recently highlighted the concern that cancer itself causes generalized distress in the forms of sadness, anger, and worry and that these symptoms are conflated with PTSD [13]. Another concern is that factor structures of PTSD scales in cancer populations have not always conformed to the three-factor structure of PTSD [15]. One study found numbing and avoidance as separate symptoms, inconsistent with DSM-IV symptomatology, and weak factor loadings [16]. However, other studies from non-cancer settings have also found a four-factor structure for PTSD scales (e.g., [17; 18]). Therefore, there is significant debate as to whether cancer conforms to the traditional picture of a trauma causing PTSD.

In the literature, the proportion of cancer survivors with PTSD has varied widely, from 36-45% of ovarian cancer survivors [19] to 6% of breast cancer survivors [20].

Andrykowski and Cordova [21] found that time since the end of treatment, stage of cancer at diagnosis, and psychosocial factors such as social support predict levels of PTSD. Other studies have since confirmed that sources of this variation may include clinical factors such as time since diagnosis [22] and stage of disease [23] or demographic factors such as age [24] and gender [25].

Family members or caregivers of cancer survivors may also experience negative psychosocial outcomes, such as anxiety and depression [26; 27]. Family caregivers of cancer patients have a poorer quality of life than cancer patients themselves [28]. Ell et al. [29] found that individuals close to cancer survivors were still experiencing distress related to the cancer a year after their family member's diagnosis. Smith [11] found that parents of cancer survivors have a greater risk of PTSD than their children. These studies are concordant with a systemic approach to illness, which assumes that the cancer experience takes place within a social system of delicate dynamics and interrelationships [30]. In line with this literature, we decided to include studies sampling family members and caregivers of cancer survivors in our review.

This review contributes to the debate about whether cancer can function as a traumatic stressor by identifying factors significantly affecting the reported proportion of a post-cancer diagnosis sample with PTSD, expressed as a percentage. We also calculate the relative likelihood of PTSD in cancer survivors compared to controls without cancer. We assessed current PTSD, rather than lifetime PTSD, as studies investigating the latter were uncommon. This review includes studies applying DSM-IV or International Classification of Diseases (ICD) version 10 criteria for PTSD to adult cancer survivors at any stage of disease, from one month after diagnosis to many years after treatment has ended. DSM-IV and ICD-10 criteria for PTSD are closely related, including the same three symptom clusters, although the ICD-10 criteria require the traumatic event to be likely to cause "pervasive distress in

almost anyone" [31] while DSM-IV criteria require "fear, horror, and helplessness" [8; 32]. We have applied "Preferred reporting items for systematic reviews and meta-analyses" (PRISMA) guidelines [33] and the "Meta-analysis of observational studies in epidemiology" (MOOSE) guidelines [34].

Methods

Literature search strategies

The first stage of the literature review process was to query three databases: MedLine via PubMed, the Published International Literature on Traumatic Stress (PILOTS) database via ProQuest, and PsycInfo via ProQuest. All databases were searched using a combination of free text key words and controlled vocabulary terms (for example, MeSH) for two concepts: cancer and post-traumatic stress disorder. The full search strategy for the MedLine search is given in Table 1.

[Table 1]

We searched within one journal in particular, Psycho-Oncology, for all articles containing the term "post-traumatic stress" or its variants. From the papers identified using these methods, we created a list of authors who had contributed multiple papers. We contacted these authors for citations that we might have excluded. Authors were asked to advise us of any well-known papers as well as rare or unpublished papers, in order to address the "file drawer" problem. We identified a subset of highly relevant papers and conducted backward and forward literature searches, searching reference lists and the ISI Web of Knowledge cited reference search function. To identify grey (or "fugitive") literature, we also searched an online database called OpenGrey. The systematic review protocol can be obtained from the first author. All papers published before ICD-10 and DSM-IV criteria were published in 1994 were excluded. Literature indexed after mid-2013 was excluded, as newer

DSM-5 criteria came into force after that point. Where there was an option to include specific subheadings of a search term, we included all possible subheadings. A PRISMA flowchart demonstrating the search process can be found in Figure 1. Papers were assessed for eligibility using the inclusion criteria in Table 2.

[Figure 1]

[Table 2]

Quality assessment

We undertook quality assessment of included papers using Loney et al.'s [35] criteria for the assessment of epidemiological studies. This eight-item checklist assesses criteria relating to the selection of the sample, the measurement of the outcome, and the description of the results. As most of the studies identified for this review were retrospective or cross-sectional cohort studies, none met all eight criteria. Quality scores are shown in the quality criteria table, Supplementary Materials 3. No study adjusted for known risk factors for PTSD, such as age or gender [24; 25].

In addition to this formal quality assessment, we focused on potential sources of bias in estimates of PTSD proportion; for instance, we excluded papers that sampled from support groups and other settings for which the proportion of PTSD would be exaggerated, since seeking help is associated with greater severity of mental health problems [36; 37]. Twelve papers were excluded based on this criterion. These papers sampled from among participants pre-screened for high or low PTSD or depression scores; those identified by clinicians as having high levels of distress; those referred to or seeking counseling, psychology, or support services; and groups of participants with known psychiatric illness.

Data extraction

Information extracted from studies meeting inclusion criteria included: number of people with PTSD; sample size; PTSD measurement instrument; type of cancer; type of treatment; stage of cancer; mean time since diagnosis in months; country; gender; mean age of sample; whether the study was peer-reviewed or not; reliability of PTSD instrument; whether the sample included survivors or family members/caregivers; ethnicity; prior trauma; whether the PTSD was explicitly linked to cancer; or whether "post-traumatic stress" or any variant were included in the title or abstract of the paper. This list of variables was derived from previously identified risk factors [12]. For papers reporting estimates of PTSD in cancer survivors compared to non-cancer controls, we also extracted the number of people with PTSD in the non-cancer group and the size of this group. When only abstracts were available, we contacted authors for further information and extracted all information possible from abstracts.

Authors were contacted for missing data if the papers did not report the number of people with PTSD. For longitudinal studies, we included only the latest data point available for all papers in order to take advantage of the longer latencies between diagnosis and PTSD assessment. This also allowed us to avoid double-sampling participants. If papers reported two methods of assessing PTSD, we included only the results from clinical interviews rather than self-report measures. Where authors reported time since the end of treatment, we added six months to derive an approximation of the time since diagnosis. Where medians rather than means were given, the data were considered missing.

Statistical procedures

We conducted random effects meta-analysis using Comprehensive Meta-Analysis 2.0 (Englewood, NJ, 2005) and Stata version 14.1 (StataCorp 4905 Lakeway Dr College Station,

TX 7784). We used random effects rather than fixed effects because, in this case, it was reasonable to assume that the proportion of survivors with PTSD would not be uniform across all studies. We used the DerSimonian-Laird [38] estimator for between-study variance. We calculated I^2 to determine the amount of heterogeneity [39]. For studies comparing cancer survivors to controls with no cases of PTSD in the control group, 0.25 was added to the denominator of the odds ratio to avoid a denominator of 0. All subgroup analyses were planned according to our pre-specific protocol.

Factors affecting proportion of PTSD

Since the log proportion effect sizes represent single values, and not a comparison of values, investigation of variables influencing effect sizes would not appropriately be called "moderator analysis." However, we sometimes refer to it as such because this is the normal usage in meta-analyses. We conducted mixed-effects moderator analysis and "method of moments" (random effects) meta-regression to determine factors affecting the proportion of people with PTSD in a sample. Potential "moderators" included PTSD assessment tool (self-report or clinical interview), type of cancer, type of treatment, stage of disease, time since diagnosis, global region, gender of sample, mean age of sample, whether the study was peer-reviewed or not, and the relationship of participants to the survivor (in samples of family members). In response to literature asserting that self-report measures overinflate estimates of PTSD, we extracted information about type of PTSD measurement instrument and conducted moderator analyses to identify differences between measurement instruments in terms of PTSD proportion.

Reliability analysis

Reliability analysis was conducted both for study selection and data extraction. A second coder was asked to apply inclusion criteria to 10% of screened papers and determine whether

they were eligible for this study; agreement was 93.8%. The two discrepancies were due to one of the coders missing information from the articles. A second coder was also asked to extract data from 10% of all studies included in the analysis. Of 108 items extracted, the coders agreed on 102 (94.4%) of items. Four of these discrepancies were due to the second coder missing information in the papers.

Results

Description of studies

We identified 120 samples from 110 studies meeting inclusion criteria. These studies included 16,755 participants, 1,812 of whom were diagnosed with PTSD according to individual study procedures for assessing PTSD, equivalent to an overall absolute proportion of 10.8%. Proportion of the sample with PTSD ranged from 0% to nearly 52%. Hematological, breast, prostate, colorectal, gynecological, brain, and head and neck cancers were represented. The majority of studies were conducted in North America. The authors of an additional 70 papers were contacted for missing data, but were either unable to provide data or did not respond to our request for missing data. A table of all included studies and full reference information is shown in Supplementary Materials 1. Estimates of PTSD proportion in ascending order along with their confidence intervals are shown in Figure 2.

[Figure 2]

Publication bias was assessed using a plot of the observed PTSD proportion and the standard error of the estimate, as shown in Figure 3. This indicates the presence of bias, as the less powerful the study, the higher the reported proportion of PTSD. For further discussion of bias, please see Supplementary Materials 2.

[Figure 3]

Summary odds ratio

Of the 110 studies meeting eligibility criteria, eleven studies (twelve samples) included a comparison group. We used random effects meta-analysis on this subset of twelve samples to calculate log odds ratios for PTSD for cancer survivors compared with controls who had no history of cancer. The summary odds ratio was 1.66 (95% CI: 1.09, 2.53). The Q test for heterogeneity was not significant; I^2 was 17.2%, indicating that relatively little variability between studies was attributable to heterogeneity. A forest plot illustrating effect sizes for each study and confidence intervals can be found in Figure 4. Odd ratios comparing occurrence of PTSD in cancer survivors compared to non-cancer controls are generally larger than 1, indicating a higher likelihood of PTSD among cancer survivors.

[Figure 4]

In addition, we calculated the rate difference between non-cancer controls and cancer survivors. The summary rate difference was 6.2% (95% confidence interval 1.6% to 10.8%), although analyses of bias, as described in Supplementary Materials 2, indicate that this estimate of difference may be inflated. A forest plot of the rate differences can be found in Figure 5. A funnel plot demonstrating publication bias affecting these twelve comparison studies is shown in Figure 6.

[Figures 5 and 6]

Factors affecting reported proportion of sample with PTSD

The above odds ratio reflects the relative likelihood of PTSD among cancer survivors compared to controls without a history of cancer. We also conducted analyses to determine the factors affecting the raw proportion of cancer survivors with PTSD within each sample. The following analyses are based on all studies that reported sufficient information on these

variables. Since not all studies reported on all potential factors, the numbers included in each separate analysis may differ.

Measurement instrument

Eighty-two studies reported the proportion of PTSD as assessed by self-report measures and 31 assessed this figure through clinical interviews. Type of measurement instrument (clinical interview compared to self-report measure) had a significant effect on proportion of cancer survivors reporting PTSD ($Q(1) = 24.8$, $p < 0.001$). The percentage of people with PTSD assessed using clinical interviews was 4.0% (95% CI: 2.6%, 6.2%), while the percentage of people with PTSD assessed using self-report measures was 12.8% (95% CI: 10.8%, 15.0%).

Type of cancer

We also performed moderator analysis to determine whether type of cancer significantly influenced PTSD proportion. Moderator analysis indicated that there was a significant difference in terms of PTSD proportion across cancer types ($Q(6)=16.2$, $p = 0.013$). Table 3 below shows the summary proportion of the sample with PTSD for each type of cancer. However, the number of studies may skew results; for instance, there is only one study reporting on head and neck cancers, which reported a relatively low percentage of PTSD cases.

[Table 3]

Type of treatment

Moderator analysis indicated that there was a significant difference in terms of PTSD proportion across types of treatment ($Q(3)=13.3$, $p = 0.004$). Table 4 below shows the summary proportion estimate for each type of treatment.

[Table 4]

Geographic region

There was a significant difference in terms of PTSD proportion depending on the region where the data were collected ($Q(3)=68.9$, $p < 0.001$). Table 5, below, shows the summary proportion estimate for each geographic area.

[Table 5]

Whether "post-traumatic stress" was in the title or abstract

We extracted data regarding whether "post-traumatic stress," PTSD, or any other variant of the term was in the title or abstract of the paper. Summary proportions of the sample with PTSD were significantly higher among those papers that did contain these terms in the title ($Q(1) = 17.8$, $p < 0.001$). Papers containing these terms in the title or abstract reported a proportion of PTSD of 12.2% (95% CI: 10.4, 14.2) compared to studies that did not contain these words in the title or abstract, which reported a summary proportion of 2.8% (95% CI: 1.4, 5.5).

Prior trauma

One hundred fourteen studies reported estimates of PTSD among samples that had not experienced a prior trauma, and six papers reported estimates of PTSD among cancer survivors who had experienced a prior trauma. PTSD estimates were significantly higher among the samples who had experienced a prior trauma ($Q(1) = 6.1$, $p = 0.014$). Proportion with PTSD of the samples of survivors who had experienced a trauma prior to cancer was 19.4% (95% CI: 11.7, 30.4). Among the samples who had not experienced a prior trauma, the summary proportion of PTSD was 9.9% (95% CI: 8.4, 11.6).

Age

Mixed effects ("method of moments") meta-regression demonstrated that the mean age of the sample was significantly related to log proportion with PTSD. Among papers

reporting higher mean sample ages, proportion of sample with PTSD was lower. The slope of this relationship was calculated from raw, rather than logit, proportions. The slope indicated that, for each additional year increase in the mean age of a group, PTSD estimates would be predicted to decrease by 0.3%.

Time since diagnosis

Mixed effects meta-regression also demonstrated that time since diagnosis was negatively related to log proportion. Among papers that reported longer latencies between diagnosis and data collection, PTSD proportion was lower. As above, the slope of this relationship was calculated from raw proportions. The slope indicated that, for each additional year after diagnosis, PTSD percentage within a sample would decrease by 0.5%.

Factors that did not influence proportion of PTSD

No other variables significantly influenced proportion of the sample with PTSD. This includes stage, gender of sample (where the gender was entirely male or female), and whether or not the study was reported in a peer-reviewed journal. Family members/caregivers of relatives with cancer survivors did not differ from cancer survivors themselves in terms of the proportion of the sample with PTSD. Forty-nine studies specifically assessed PTSD related to cancer, and these did not differ significantly in terms of proportion with PTSD from studies which did not explicitly link PTSD to the cancer experience.

Discussion

This systematic review and meta-analysis assessed the relative likelihood of PTSD among cancer survivors compared to controls and the factors influencing the proportion of cancer survivors with PTSD. Among the twelve comparative studies we found, cancer survivors seem to have 1.66 times the odds of PTSD compared to controls who have not had cancer. In many of these studies, control participants were potentially traumatized as well,

with some having non-malignant disease [e.g., 25] or having siblings with cancer [40]. This may imply that this study underestimates the odds ratio. Publication bias might, however, have a countervailing effect, as shown in the analyses of bias in Supplementary Materials 2.

The results of this meta-analysis should be interpreted in light of the recent changes to the PTSD diagnosis described in the DSM-5 [9]. The DSM-5 no longer includes medical illness as a potential traumatic event, but the present meta-analysis shows that, at least according to the earlier DSM-IV criteria for PTSD, cancer survivors and people close to them may have post-traumatic stress related to their illness. There are several studies cited in this review that used clinician-administered diagnostic interviews to assess PTSD as specifically related to cancer. These results call into question any clear delineation between a "traumatic" event and a merely "upsetting" event. However, it is also relevant to note that cancer survivors may still meet criteria for "adjustment disorder." Akechi et al. [41] have shown that the prevalence of adjustment disorder among cancer survivors exceeds that of PTSD; Hund et al. [42] estimate this prevalence at 12.4%. Therefore, it is a matter of ongoing controversy whether the category of adjustment disorder, rather than post-traumatic stress disorder, better describes cancer survivors' experiences after their disease.

Our results must be interpreted in light of the broader range of changes made to the PTSD diagnosis within DSM-5 [9]. According to DSM-5, medical illness no longer counts as a traumatic event, and the subjective criteria of "fear, horror, and helplessness" are no longer necessary. However, DSM-5 PTSD also requires a different constellation of symptoms; for instance, while DSM-IV required avoidance and emotional numbing symptoms, DSM-5 requires avoidance symptoms as separate from a new category of symptoms referred to as "negative cognitions." Kangas [43] discusses the implications of these changes for future diagnoses of PTSD among a cancer population, showing that the DSM-5 criteria for PTSD may not readily apply to cancer survivors, as many of their negative cognitions are related to

future-oriented worries and concerns rather than memories of the past. Therefore, the prevalence of DSM-5 PTSD among cancer survivors is uncertain.

It is important to mention that our meta-analysis compared the proportion of people with PTSD within varying post-cancer samples across different factors, but these proportions do not easily translate into overall prevalence figures. To determine the overall prevalence of PTSD among cancer survivors, we would need to have synthesized data from across large, population-based epidemiological studies. Unfortunately, few such studies exist. However, many studies reported a raw proportion of the total sample with PTSD; these are the figures that we have synthesized in our review and the types of papers that we included. Given the variations in quality and representativeness of these studies, this paper is a step towards understanding the factors that influence these raw proportions of PTSD among diverse cancer samples, but it cannot establish an overall figure for the prevalence, at the population level, of PTSD after a diagnosis of cancer.

Our study had several limitations. First of all, a high number of potentially eligible studies were excluded because of missing data. This was partly due to the fact that many studies were nearly twenty years old, and in many cases data were not retained for such a long period. Furthermore, this study provides a synthesis of proportion of cancer survivors with PTSD, since that was the measure of PTSD most frequently reported. As a result, the studies included in this review assessed current PTSD rather than lifetime PTSD. We found very few studies assessing lifetime risk of cancer-related PTSD. Therefore, the above results may be taken as an indication of how many cancer survivors are currently living with PTSD, but it does not tell us how many cancer survivors have ever had PTSD or how many cancer survivors are likely to experience PTSD at any time after diagnosis. Furthermore, few studies assessed the impact of traumas in the period intervening between diagnosis and the measurement of PTSD symptoms, although our finding that proportion with PTSD decreases

as time since diagnosis increases suggests that participants did not experience many traumas in this period.

Relatedly, most of the studies included in this review were cross-sectional; few studies were prospective or longitudinal. This is important because cross-sectional studies such as those included in our review cannot give likely timeframes for the development of PTSD nor, as described by Kangas et al. [10], can they illuminate its potential course. Our results, in part, reflect a lack of prospectively designed studies. Therefore, our results reflect the likelihood of having PTSD at specific points after diagnosis based on different variables, but not the cumulative likelihood of developing PTSD after diagnosis. In addition, although many studies linked post-traumatic stress directly to the cancer experience, for some others, it was not clear whether PTSD was present before the cancer diagnosis. This may be seen as a limitation of the study, because this implies that some cases of PTSD might have been present before a cancer diagnosis. However, the proportion of the sample with PTSD did not seem to differ among papers indexing PTSD directly to the cancer experience and papers for which this was unclear. We believe that this is because many studies in the latter category did, in fact, index PTSD to the cancer experience, although this linkage was not formally reported.

There may be interactions between variables considered separately in this analysis. For example, as above, three papers reported very high estimates of PTSD after chemotherapy. However, these studies used self-report measures, and a fourth study on PTSD after chemotherapy as assessed by clinical interview reported a much lower figure. It is difficult to determine whether the higher figures are attributable to chemotherapy or to the use of self-report measures. From this collection of cross-sectional studies, it is difficult to determine whether or not such measurement error has occurred in this analysis. Related to this point, it is also the case that there were often unequal numbers of studies reporting on

different levels of moderator variables. This is a common occurrence in meta-analysis, as papers occur in varying frequency in the literature. However, in our study this may constitute a limitation, as it is unclear whether, for instance, the three studies reporting on PTSD after radiotherapy are representative.

We expected that clinical variables, such as type of cancer and stage of disease, would be particularly important in determining the proportion of cancer survivors with PTSD. Our results indicate that there are significant differences in terms of PTSD proportion across cancer types, but this result should be interpreted with caution, given that some types of cancer are under-represented. For instance, 38 studies (over half of the studies specifying a particular type of cancer) reported on PTSD after breast cancer, but only one study reported on PTSD after head and neck cancer. Colorectal cancers, the third most common cancer in both men and women in the United Kingdom [44], are represented by only two studies. Therefore, there seems to be a disproportionate focus on breast cancer in the literature on post-traumatic stress, and more research is required to determine whether PTSD figures vary across cancer types.

PTSD proportion also differed by type of treatment. Surgery seemed to be associated with a lower proportion of PTSD after cancer diagnosis; this may be because, in some cases, radical surgery can remove cancer without the need for more invasive treatments. However, chemotherapy was associated with a greater proportion of PTSD. One explanation for this may be that chemotherapy can cause chronic or repeated toxicity rather than the more immediate and acute pattern of distress associated with surgery. The DSM-5 [9] emphasizes that repeated or continuous traumas may trigger post-traumatic stress in the same way as sudden, unexpected traumas. In line with this, chemotherapy may act as a prolonged reminder of cancer and its implications, and for this reason may be associated with a higher incidence of PTSD.

Another anomalous finding was that stage of cancer did not affect PTSD proportion. Cancers caught early are more curable and less threatening, objectively, than cancers diagnosed at more advanced stages. This is particularly relevant in light of recent changes to the diagnostic criteria of PTSD for the DSM-5 [9], which has eliminated the criteria that a trauma cause subjective "fear, horror, and helplessness." However, in contradiction to that, our results indicate that stage, an objective indicator of threat, is not associated with PTSD proportion. This implies that subjective appraisals of the trauma may be important in determining levels of post-traumatic stress, as was also found by Mehnert et al. [14].

There is debate as to whether self-report measures are sufficiently robust to be used as diagnostic tools for PTSD. On one hand, self-report scales such as the Post-traumatic Stress Checklist (PCL) have shown acceptable functionality as screening tools for PTSD [45; 46]. However, more recently, evidence has emerged that self-report measures overestimate the proportion of people reporting PTSD [47]. In response, some researchers (e.g., [48; 49]) have used self-report measures to assess post-traumatic stress symptomatology or generalized cancer-related distress, without using cut-offs for a PTSD diagnosis. Our results indicate that participants who use self-report measures are roughly three times more likely to meet criteria for PTSD than are those assessed using diagnostic interviews. This supports the view that self-report measures, while potentially useful indicators of symptomatology, should be used with caution as diagnostic tools, particularly in patients treated for cancer.

Older participants were less likely to have PTSD, which is consistent with literature on older age and post-traumatic stress [50]. Female participants did not have a higher proportion of PTSD, in contrast to previous reports [51]. This may have to do with the fact that few studies reported separate proportion figures for each gender, so we were unable to detect such differences. Additionally, some have argued that symptoms of PTSD persists over time, and that they are not necessarily a part of "natural" recovery [7]. Our results

suggest that the proportion of a sample with PTSD may be lower in studies sampling further from diagnosis, although the proportion does not fall to zero over time. Finally, groups of participants who had had a prior trauma were more likely to report PTSD, as has been reported previously in the literature [52].

We were unable to explore the effect of ethnicity upon cancer-associated PTSD as very few studies reported figures separately for each ethnic group. Anecdotally, we note that many studies reporting the ethnic breakdown of their samples reported percentages of Caucasian participants in excess of 80%. A recent study [53] has indicated that ethnicity may be an important risk factor for the development of cancer-related PTSD, but this study was ineligible for our review because it used the Impact of Events Scale, a measure that does not include all symptoms of post-traumatic stress disorder. Given evidence that marginalized groups may be disproportionately affected by trauma [54], we believe this topic requires further empirical investigation.

Estimates of the proportion of a sample with PTSD depended on several factors related to the context within which studies were performed and published. Studies conducted in Asia reported lower levels of PTSD, while studies conducted in the Middle East (mostly Israel) reported higher levels of PTSD. These differences may be attributable to cultural differences or to differing diagnostic practices; it is not clear from our study what the source of these differences is. Estimates of the proportion of PTSD were not significantly different between published studies that had been peer reviewed (n = 99) and those that had not (n = 21). However, studies containing the words “post-traumatic stress” were significantly more likely to report a higher proportion of PTSD, a possible example of confirmation bias.

Relatives and caregivers of cancer survivors had PTSD in similar proportions to cancer survivors themselves. This finding is concordant with other studies that have shown that relatives and caregivers are equally, if not more, affected by the cancer experience [e.g.,

55]. This finding is also interesting in light of the fact that the etiology of PTSD may be different for cancer survivors than it is for their significant others. According to the DSM-IV [8], an event triggering a PTSD diagnosis involves "a threat to the physical integrity of self or others." In the case of family members of cancer survivors, their PTSD is associated with traumas that are vicariously, rather than directly, experienced. Despite the difference in triggers between cancer survivors and their family members, PTSD proportions did not seem to differ between these two groups. This strengthens the argument, informed by a systemic approach to illness [30], that family members are closely involved in their loved one's illness. However, the recent changes to the DSM-5 indicate that close friends and family members of cancer survivors cannot have PTSD related to their loved one's cancer, as "indirect exposure" can only be considered under a traumatic stress framework if the trauma is "violent or accidental" [9]. Our results conflict with this assertion, showing that close friends and family members can meet criteria for PTSD even if their exposure to the trauma is indirect, at least according to DSM-IV criteria.

Our study suggests several directions for future research. Firstly, as above, further research establishing PTSD figures across a broader variety of cancer types would be useful, as research on patients with breast cancer and gynecological cancer is currently over-represented. Research on ethnicity and socioeconomic status as predictors of cancer-related PTSD is also sparse. However, these research agendas may be stymied by new DSM-5 guidelines that exclude cancer as a potential traumatic event. Further conceptual analysis of cancer-related PTSD in light of these changes should be undertaken, whether this involves deconstructing the current criteria for PTSD, or whether researchers in this area must shift focus onto the category of "adjustment disorder" rather than PTSD.

Conclusion

Cancer survivors are at increased risk of post-traumatic stress disorder, as defined according to the DSM-IV criteria for PTSD. Synthesis of the twelve eligible comparison studies shows that cancer survivors have 1.66 times the odds of PTSD compared to controls with no history of cancer. The rate difference between the two groups is 6.2%. There is little heterogeneity amongst the papers contributing to the estimate of odds ratio. This finding is noteworthy given the controversy surrounding the inclusion of cancer within a traumatic stress framework and the fact that cancer is no longer officially considered a traumatic event according to the DSM-5 [9]. Nevertheless, psychologists or other professionals providing psychosocial services should be aware of this increased risk of PTSD among cancer survivors. Younger patients, those who have had chemotherapy, and those seen sooner after diagnosis may be particularly vulnerable. Relatives and loved ones may also suffer from PTSD as often as cancer survivors themselves. Finally, cancer-related trauma may be complicated by an internal locus of threat and future-oriented cognitions, which may influence the clinical pattern of the PTSD.

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Tables

Table 1. Full electronic search strategy for MedLine via PubMed

(post-traumatic stress disorder[TIAB] OR posttraumatic stress disorder[TIAB] OR post traumatic stress disorder[TIAB] OR PTSD[TIAB] OR stress disorders, post-traumatic[MH]) AND (neoplasms[MH] OR cancer*[TIAB] OR neoplas*[TIAB] OR malignan*[TIAB] OR oncolog*[TIAB] OR tumour*[TIAB] OR tumor*[TIAB])
Filter: Adults 19+

Table 2: Inclusion and exclusion criteria for papers

Inclusion criteria	Exclusion criteria
Studies included in this review: 1. Original reports of empirical research 2. Studies assessing post-traumatic stress disorder among cancer survivors who were older than 18 at diagnosis or their caregivers/relatives 3. Studies assessing PTSD at least one month after diagnosis 4. Studies using validated instruments reflecting DSM-IV or International Classification of Diseases (ICD) version 10 criteria for PTSD 5. Studies published between 1994 (when DSM-IV criteria were published) and 2013 (when DSM-IV criteria were replaced) 6. Studies written in the English language	Studies excluded from this review: 1. Case studies or review articles 2. Studies reporting on PTSD among children younger than 18 or their relatives 3. Studies that were likely to oversample survivors with PTSD, such as studies that sampled survivors from support groups 4. Articles assessing post-traumatic stress symptoms outside of the DSM-IV or ICD-10 definitions, or failing to assess all such symptoms

Table 3: Summary proportion (%) of samples with PTSD after cancer diagnosis, shown by type of cancer

Type of cancer	Number of studies	Summary proportion with PTSD (95% CI)
Brain	3	17.4 (8.0, 33.9)
Breast	38	10.0 (8.0, 12.5)
Colorectal	2	4.3 (0.4, 31.0)
Gynaecological	15	13.2 (8.1, 20.9)
Head and neck	1	0.3 (0.0, 2.3)
Haematological	9	10.4 (6.8, 15.4)
Prostate	4	9.8 (3.4, 25.4)

Table 4: Summary proportion (%) of samples with PTSD after cancer diagnosis, shown by type of treatment

Type of treatment	Number of studies	Summary proportion with PTSD (95% CI)
Chemotherapy	4	27.0 (13.0, 47.7)
Radiotherapy	3	14.6 (6.8, 28.7)
Stem cell transplant	11	11.8 (8.5, 16.2)
Surgery	13	5.6 (3.3, 9.3)

Table 5: Summary proportion (%) of samples with PTSD after cancer diagnosis, shown by geographic region

Region	Number of studies	Summary proportion with PTSD (95% CI)
Asia	7	2.2 (0.4, 10.3)
Europe	28	9.1 (6.4, 12.7)
Middle East	6	26.3 (22.4, 30.7)
North America	50	9.1 (7.0, 11.9)

Figure legends

Figure 1: PRISMA flowchart

Figure 2. Proportions with PTSD and confidence intervals from 120 included studies, both comparative and non-comparative

Figure 3. A plot of standard error by proportion with PTSD, demonstrating publication bias in 120 samples, both comparative and non-comparative

Figure 4. Forest plot illustrating odds ratios, confidence intervals, and overall summary odds ratio representing the likelihood of PTSD after cancer diagnosis compared to non-cancer controls

Figure 5. Forest plot illustrating rate differences, confidence intervals, and overall summary rate difference, comparing cancer survivors to controls without cancer

Figure 6: Funnel plot demonstrating publication bias in 12 samples comparing estimates of PTSD proportion among cancer survivors to controls who have not had cancer